Journal of Clinical Tuberculosis and Other Mycobacterial Diseases 1 (2015) 1–12

Contents lists available at ScienceDirect

Journal of Clinical Tuberculosis and Other Mycobacterial Diseases

journal homepage: www.elsevier.com/locate/jctube

How to manage children who have come into contact with patients affected by tuberculosis

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ARTICLE INFO

Article history:
Received 23 April 2015
Revised 14 June 2015
Accepted 5 July 2015

Keywords:
Contacts
IGRA
LTBI
Mycobacterium tuberculosis
Multidrug-resistant tuberculosis
Tuberculosis

ABSTRACT

Childhood tuberculosis (TB) indicates a recent infection, particularly in children aged < 5 years, and therefore is considered a sentinel event insofar as it highlights the presence of an undiagnosed or untreated source case. The risk of acquiring TB is directly proportional to the number of bacilli to which a subject is exposed and the environment in which the contact occurred. This document contains the recommendations of a group of Italian scientific societies for managing a child exposed to a case of TB based on an analysis of the risk factors for acquiring latent tuberculous infection (LTBI) and developing the disease, and the particular aspects TB transmission during the first years of life. The guidance includes a detailed description of the methods used to identify the index case, the tests that the exposed child should receive and the possibilities of preventive chemoprophylaxis depending on the patient's age and immune status, the chemotherapy and monitoring methods indicated in the case of LTBI, the management of a child who has come into contact with a case of multidrug-resistant or extensively drug-resistant TB, and the use of molecular typing in the analysis of epidemics. The group of experts identified risk factors for tuberculous infection and disease in pediatric age as well as gave recommendation on management of contacts of cases of TB according to their age, risk factors and exposure to multidrug-resistant or extensively drug-resistant TB.

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http://dx.doi.org/10.1016/j.jctube.2015.07.002

Introduction

Childhood tuberculosis (TB) indicates a recent infection, particularly in children aged <5 years, and therefore is considered a sentinel event insofar as it highlights the presence of an undiagnosed or untreated source case [1]. The transmission of *Mycobacterium tuberculosis* is usually due to the inhalation of airborne particles or droplets containing 2–3 micro-organisms spread by the sneezing or coughing of an adolescent or adult with bacilleferous pulmonary or laryngeal TB.

It is now universally accepted that the risk of acquiring TB is directly proportional to the number of bacilli to which a subject is exposed [2]. In the first place, it depends on the characteristics of the source case: contagiousness is generally limited to subjects with lung disease, and is greater among the patients with bacilleferous forms (i.e. those with positive microscopic test results), in whom the estimated transmission rate is about 35% as against the 17% observed among those with non-bacilleferous forms [3,4]. It is also known that subjects with cavitating TB and frequent cough are more bacilliferous and contagious than those with other pulmonary pictures or who cough less frequently [5]. Furthermore, any manoeuvre capable of stimulating coughing can lead to more aerosolised respiratory secretions and consequently increase contagiousness. The subjects with extra-pulmonary disease (meningitis or abdominal, renal or bone TB) are generally considered not to be contagious, but the absence of pulmonary involvement must be documented before this can be declared [5]. Children with TB who are less than 10 years old are less frequently contagious because their pulmonary lesions are usually small and paucibacillary, and their cough is often unproductive [3,6].

The number of bacilli to which a subject is exposed is strictly related to the environment in which the contact takes place. Enclosed and poorly ventilated places favour the concentration of tubercular bacilli in the air and increase the likelihood of transmission, whereas contacts in the open air or well-ventilated environments decrease it [7]. Similarly, it is important to evaluate the time spent in an enclosed space with the source case. The effect of the combination of these two variables has been clearly shown in studies of the contacts arising during air flights [8]. Living together gives rise to the greatest exposure to TB: this has been documented in studies such as that of Singh et al. who evaluated the prevalence of TB in children living with adults with active TB and found a significant difference between those living with adults with microscopic positive or negative expectorate (respectively 68.4 and 31.6%) [6].

Only few, highly variable and conflicting data are available concerning transmission by pediatric source cases, all of which come from individual case reports: the rate of transmission when a child or adolescent has microscopic positive expectorate or gastric aspirate ranges from 0.5 to 39.3% [5], whereas the only two reported cases of children with microscopic negative expectorate/gastric aspirate transmitted TB to 29.8 [9] and 72.4% [10] of their contacts. However, the exiguous number of described cases and the lack of information concerning the presence of other risk factors for the acquisition of TB in the contacts does not allow any conclusions to be drawn concerning the real rate of transmission when the source case is a child.

This document contains the recommendations of a group of Italian scientific societies for managing a child exposed to a case of TB based on an analysis of the risk factors for acquiring latent tuberculous infection (LTBI) and developing the disease, as well as the particular evolution of TB during the first years of life.

Table 1
Quality of evidence and strength of recommendation.

Quality of evidence	
I	Evidence from more than one properly designed, randomised, controlled study and/or systematic review of randomised studies
II	Evidence from one properely designed, randomised, controlled study
III	Evidence from cohort studies or their meta-analysis
IV	Evidence from retrospective case-controlled studies or their meta-analysis
V	Evidence from case series without control group
VI	Evidence from opinions of respected authorities, based on clinical experience
Strenght of recommendation	
A	The panel strongly supports a recommendation for use
B	The panel moderately supports a recommendation for use
C	The panel marginally supports a recommendation for use

Methodology

The Consensus Conference method was used, following the National Institutes of Health and the National Plan Guidelines as previously reported (Table 1) [11,12]. Relevant publications in English were identified through a systematic review of MEDLINE and the Cochrane Database of Systematic Reviews from their inception through December 31, 2014. Search strategy:"children[Title/Abstract] OR pediatric[Title/Abstract]) OR paediatric[Title/Abstract]) AND tuberculosis[Title/Abstract]) AND English[lang])". The Working Group agreed on a list of clinical problems relevant to the management of children at risk of, or exposed to TB. The evidence review procedures focused on patients aged 0–18 years and included section-specific targeted searches as well as formal systematic reviews on selected topics. In addition, the clinical recommendations reported in relevant and updated international guidelines have been reviewed and critically compared in case of debated issues. All the data were included in tables of evidence for each topic. Trained personnel performed the critical appraisal of the acquired literature using the Scottish Intercollegiate Guidelines Network methodological checklists [13]. Subsequently, the bibliographical material and a preliminary draft of the document were provided to the panel members. In the various meetings, literature evidence was reported and discussed and the Delphi method was used to reach a consensus when the evidence did not provide consistent and unambiguous recommendations [13]. The final text was revised on the basis of these discussions and submitted by e-mail to participants at the Consensus Conference for final approval. The multidisciplinary panel of clinicians and experts in evidence-based medicine were identified with the help of the participating scientific societies. Specifically, the panel included experts in the fields of general pediatrics, pediatric infectious diseases, infectious diseases, pneumology, microbiology, radiology and methodologists and was coordinated by the Italian Society of Pediatric Infectious Diseases (SITIP). No panel member declared any

Italiana di Infettivologia Pediatrica (SITIP), represented by Susanna Esposito, Maurizio de Martino, Luisa Galli, Alfredo Guarino, Laura Lancella, Andrea Lo Vecchio, Nicola Principi, Samantha Bosis, Elio Castagnola, Clara Gabiano, Silvia Garazzino, Giuseppe Losurdo, Carlotta Montagnani, Martina Anziati, Beatrice Ascolese, Sabrina Becciani, Laura Cursi, Annalisa Grandin, Daniele Le Serre, Caterina Marabotto, Irene Raffaldi, Giulia Remaschi, Riccardo Scotto, Laura Senatore, Sara Sollai, Claudia Tagliabue, Chiara Tersigni and Elisabetta Venturini; Società Italiana di Pediatria (SIP), represented by Alberto Villani, Cristina Russo and Paolo Tomà; Società Italiana di Malattie Respiratorie Infantili (SIMRI), represented by Filippo Bernardi; Società Italiana di Immunologia e Allergologia Pediatrica (SIAIP) represented by Gianluigi Marseglia and Amelia Mascolo; Società Italiana di Pediatria Preventiva e Sociale (SIPPS), represented by Giuseppe Di Mauro and Elena Chiappini; Società Italiana per le Cure Primarie Pediatriche (SiCUPP), represented by Angela Pasinato; Società Italiana di Malattie Respiratorie (SIMER), represented by Francesco Blasi, Marialuisa Bocchino and Luca Assante; Associazione Italiana Pneumologi Ospedalieri (AIPO), represented by Luigi Codecasa; Società Italiana di Malattie Infettive e Tropicali (SIMIT), represented by Alberto Matteelli; Associazione Microbiologi Clinici Italiani (AMCLI), represented by Enrico Tortoli; Società Italiana di Chemioterapia (SIC), represented by Elisa Bertazzoni; Società Italiana di Farmacologia (SIF), represented by Francesco Scaglione; STOP TB, represented by Daniela Cirillo, Marino Faccini, Giovanni Battista Migliori, Marina Tadolini, Rossella Centis and Lia D'Ambrosio; Società Italiana di Scienze Infermieristiche Pediatriche (SISIP), represented by Filippo Festini and Daniele Ciofi; MOIGE, represented by Elisabetta Scala.

conflict of interest considering the guideline topics. The panel met on three occasions, and many of the consultations involved in the document development took place interactively by e-mail or telephone contact.

When should childhood TB be suspected?

Tuberculous infection should be suspected in the presence of two not mutually exclusive conditions: (1) conditions of social/familial/epidemiological risk that may have exposed even an asymptomatic child to a high risk of infection; and (2) the presence of the typical symptoms and signs of the disease even in subjects considered to be at low risk [1]. However, given the re-emergence of the infection and the potential seriousness of TB for the health of the patient and that of the general public, the possibility finding oneself facing a case of TB must always be considered.

The principal risk factors are described below.

Factors related to exposure

In case of contacts with a patient affected by TB (most of whom are adults), the absence of symptoms is not enough to rule out TB in children and it is always necessary to take the type of contact and other risk factors into account [14-16].

A recent meta-analysis [17] has shown that contact with expectorate-positive TB patients is a factor indicating a similar risk of infection in both high-income (odds ratio [OR] 3.3; 95% confidence interval [CI] 2.2–4.8) and low-income countries (OR 3.3; 95% CI 2,2–5.1).

The risk of acquiring tuberculous infection is particularly high in children who live with expectorate-positive adults (relative risk [RR] 6.78; 95% CI 3.51–13.10) or adults with cavitating lesions revealed by chest X-ray (RR 2.45; 95% CI 1.60–3.76), or in those who have close contacts with drug users (RR 1.81; 95% CI 1.03–3.19) [18,19]. Children whose families include women with TB are exposed to an even higher risk (RR 1.34; 95% CI 1.34–3.14), probably because their contacts are more frequent than in the case of male relatives [18].

One case-control study carried out in Thailand found that the risk of developing the disease was high in children having any kind of contact with TB patients (very close: OR 85.67; 95% CI 33–647.79; $p < 0.001$; close: OR 31.11; 95%CI 4.18–255.94; $p = 0.001$; not close: OR 32.70; 95% CI 4.18–255.94; $p < 0.001$) [20].

An increased risk of thoracic TB has been found in children living with adults affected by cancer (OR 2.46; 95% CI 1.14-7.37; $p = 0.005$) [21], which indirectly suggests that the risk of developing TB may also be increased in children living with patients with chronic diseases capable of altering their immune status.

Socio-economic and environmental factors, and factors related to origin

The clinical evaluation of children with suspected tuberculous disease should be completed by an assessment of the socio-economic characteristics of their immediate families because children living in disadvantaged, precarious or economically insecure conditions are at greater risk of developing infections – and TB is no exception.

Living arrangements and housing conditions play an important role: a case-control study carried out in Bangladesh found that co-dwellers were protected against transmission if there were < 2 people per bedroom (OR 0.29; 95% CI 1.79–6.03; $p < 0.0001$), if the kitchen was separated from the bedroom (OR 0.35; 95% CI 0.2–0.62; $p = 0{,}001$), and if the home was adequately ventilated (OR 0.25; 95% CI 0.13–0.49; $p < 0.0001$) [15]. The risk of transmission is also affected by overcrowding and the economic conditions of the family (OR 1.35; 95% CI 1.06–1.72; $p < 0.017$) [20,22,23], as well as by an inadequate supply of food (OR 1.52; 95% CI 1.15–2.02; $p < 0.003$) [23].

In terms of parental socio-cultural status, children whose mothers are illiterate (OR 2.65; 95% CI 1.45–4.86; $p = 0.002$) [15] or have only received primary or lower secondary education ($p = 0.01$) are at greater risk of contracting TB [24], whereas living in a family with an adequate annual income is a protective factor (OR 0.47; 95% CI 0.28–0.77) [14].

The only environmental risk highlighted by many studies is passive exposure to cigarette smoke, which was found to lead to a more than 7-fold increase in the risk of childhood TB in a prospective study carried out in India (OR 7.43; 95% CI 1.12–49.47; $p = 0.04$) [24]. Another study has shown that the risk of TB is very high in children in very close contact with smokers (OR 6.42; 95% CI 2.13–19.93; $p < 0.001$), but not in those whose contacts are less close (OR 0.55; 95% CI 0.25–1.23; $p = 0.146$) [20]. Finally, a South African study showed that patients living with two or more smokers are at increased risk of having a TST result of > 5 mm (OR 2.79; 95% CI 1.30–5.97; $p = 0.0085$), > 10 mm (OR 2.66; 95% CI 1.28–5.25; $p = 0.0085$) or > 15 mm (OR 2.94; 95% CI 1.44–6.00; $p = 0.003$) [20], whereas the consumption of fruit and vegetables 5–7 times a week seems to be a protective factor (OR 0.38; 95% CI 0.16–0.92; $p = 0.03$) [20].

Origin and ethnicity should also be carefully investigated when drawing up the history of patients with suspected TB as migrants from areas in which TB is endemic are often infected and therefore at risk of developing the disease after settling in countries in which endemicity is low.

A study carried out in the United States between 1994 and 2007 recorded incidence rates that were about ten times higher in children of foreign origin: the risk was similarly distributed across pediatric age groups, with rate ratios of 12.9 in those aged < 1 year, 10.9 in those aged 1–4 years, 15.4 in those aged 5–12 years, and 18.58 in those aged 13–17 years [25]. A similar study carried out in North Carolina analysed incidence rates between 1994 and 2002 on the basis of the patients' ethnic origin, and found that the incidence of TB was higher among hispanics (4.5 × 100,000 person/years; $p = 0.01$) and non-hispanic blacks (3.0 per 100,000 person/years; $p = 0.003$) than among non-hispanic whites (0.2 per 100,000 person/years) [19].

A Canadian study found that an independent risk factor was coming from south–east Asia (OR 2.41; 95% CI 1.15–5.06), the eastern Mediterranean area (OR 2.65; 95% CI 1.23–5.69), central Europe (OR 3.00; 95% CI 1.18–7.64), the western Pacific area (OR 3.44; 95% CI 1.67–7.08), Latin America (OR 4.03; 95% CI 1.93–8.39) or African countries with a high (OR 3.90; 95% CI 1.57–9.73) or low prevalence of HIV (OR 3.00; 95% CI 1.33–6.78) [26].

Although the published data do not distinguish patients on the basis of age, some ethnic groups are not only at greater risk of contracting TB, but are also more likely to develop extra-pulmonary and miliary TB [27], as well as drug-resistant forms [28]. It is therefore possible to outline a socio-economic and cultural profile of the children at considerably higher risk of developing TB and experiencing worse outcomes: those living in hygienically and economically inadequate conditions characterised by overcrowding and close contacts with multiple adults, and often belonging to families of no fixed abode.

What are the risk factors for the development of childhood TB?

Only about 5–10% of subjects with primary *M. tuberculosis* infection develop active disease [29]; in the other 90–95%, the infection (which remains latent) is contained by the immune system, and so they are asymptomatic and non-contagious [29]. Once contagion has occurred, the risk of progression to tuberculous disease is highest during the first six weeks, declines exponentially over the next seven years, and then remains more or less constant for the rest of life [5]. The risk of progression also depends on age: the risk of developing active disease is significantly higher in children than in adults, being about 15% in adolescents, 24% in children aged 1–5 years, and 40–50%

Table 2
Groups of children and adolescents at greater risk of developing active TB.

- Children (particularly those aged < 5 years)
- Patients with HIV infection, or another congenital or acquired immunodeficiency
- Subjects with selective genetic defects affecting the signalling pathways mediated by IL-12 and IFN-γ
- Patients with diabetes mellitus
- Patients undergoing prolonged corticosteroid therapy (>4 weeks)
- Patients receiving other immunosuppressive treatments with anti-blastic or anti-rejection agents, or TNF-α antagonists
- Patients with haematological diseases or diseases of the reticulo-endothelial system
- Patients with severe chronic renal insufficiency
- Patients with chronic malabsorption syndrome
- Smokers
- Subjects with a low body weight and/or malnutrition

in those aged < 2 years [5]. Furthermore, the tendency to evolve into active disease is more frequent in children and its clinical course is more rapid, and (particularly if they are aged < 2 years) children are at greater risk of developing the more severe forms such as tubercular meningitis or miliary TB [29].

It has been found that the risk of progression to active disease is increased in immunocompromised subjects, particularly those with impaired cell-mediated immunity, such as those with HIV infection or congenital T cell immunodeficiency, and those treated with immunosuppressants or chemotherapeutic drugs (Table 2). In particular, HIV-infected subjects and those whose immunity is severely impaired have a 20–40 times greater risk of developing TB than the general population [30], and it is clear that the risk of clinical progression is even higher in immunocompromised children and children who also have concomitant conditions such as malnutrition or diabetes [30].

Finally, the findings of epidemiological and genetic studies suggest that there are genetically determined conditions that make certain individuals susceptible to tuberculous disease. It is thought that some carriers of mutations in the genes encoding interleukin(IL)-12 beta and beta-1 receptors or interferon(IFN)-γ receptors 1 and 2 (important receptors in the IL-12/IL-23/IFN-γ axis) are more susceptible not only to TB, but also to non-tuberculous mycobacteriosis, which is usually not pathogenic in immunocompetent subjects [31-33].

How should a child who has come into contact with a case of TB be managed?

Numerous studies have highlighted the fact that investigating the contacts of patients is a valuable means of identifying new cases of TB [5]. In less endemic countries such as Italy, the disease is mainly controlled by preventing the transmission of *M. tuberculosis*, which involves isolating contagious subjects, starting treatment as early as possible, and preventing the progression of LTI to active TB. Reporting new cases to the public health authorities is essential in order to trace people who have been in contact with them.

Contact tracing makes use of a method based on concentric circles in which priority is established by considering the duration of exposure to the index case during the period of contagiousness and the environmental conditions in which it occurred [5]. The search first considers close contacts and those known to be at risk and, if the prevalence of infection among these is higher than in the general population or the index case is highly contagious, should be extended to include regular and finally occasional contacts.

If a case of TB occurs in a school, the people responsible for surveillance should visit the school in order to evaluate its structural characteristics and logistical situation, and obtain a schedule of the curricular and extra-curricular activities of the teachers, ancillary staff and pupils [5]. If a pupil is diagnosed as having respiratory TB, priority should be given to evaluating all of the other attending the same teaching classes; if the same diagnosis is made in a teacher, priority should be given to evaluating the pupils who have attended the teacher's lessons during the previous three months. The need to include the pupils, teachers and ancillary staff of other classes should be decided on the basis of: (1) the results of the screening of the high-priority subjects described above; (2) the degree of contagiousness of the index case; (3) the length of time spent with the index case; (4) the contacts' susceptibility to infection; and (5) closeness of the contact.

If the index case is aged ≤5 years and the source of contagion has not been identified among family members, it should be sought among all of the personnel of the child's day/play school environment; if the index case is more than five years old, consideration should be given to the need to seek the source at the child's school if there is evidence supporting this possibility or if there is nothing to suggest the presence of the source elsewhere [5].

Hospitalised patients or institutional resident who are accidentally exposed to a case of respiratory TB should be concentrically screened with priority being given to those who have spent at least eight hours in an enclosed space with the index case and those at increased risk of disease progression [5].

The main aims of screening children who have come into contact with a case of TB are: (1) to identify those who are symptomatic (i.e. children of any age with undiagnosed tuberculous disease; and (2) to give prophylaxis to susceptible subjects (i.e. asymptomatic children aged ≤5 years who have been in close contact with a microscopic positive case of pulmonary TB but who do not have active disease, and immunocompromised children).

The best methods of screening contacts for TB are tuberculin skin testing (TST), an IFN-γ release assay (IGRA) and chest radiography [1,31].

Children aged ≤5 years and severely immunocompromised subjects who have been screened as indicated above should undergo a complete clinical examination including a chest X-ray even in the case of negative TST and IGRA results [5]. An IGRA is recommended for subjects who have been vaccinated with BCG in order to confirm/exclude the presence of TB in subjects with a positive TST; it is also recommended for the same reason in HIV-infected subjects. Its use as an alternative to a TST is not supported by the currently available evidence.

In the case of contact screening, a TST is considered positive when it reveals an induration with a diameter of ≥5 48–72 h after inoculation (or a diameter of > 10 mm if the child has been BCG vaccinated) [1,34,35]. All contacts who are TST and/or IGRA positive should undergo chest radiography.

TST-positive contacts should undergo chest radiography and be clinically monitored.

Children with **positive TST and/or IGRA results and a chest X-ray compatible with TB** should undergo microbiological investigations.

Children with **positive TST and/or IGRA results and a normal chest X-ray** are considered infected and should therefore be treated for LTBI.

In the management of children aged ≤5 years who have been exposed to a case of respiratory TB, the purpose of the TST or IGRA and chest X-ray is to exclude tuberculous disease [5]. **If the initial test (TST or IGRA) and the chest X-ray are both negative,** primary chemoprophylaxis should be started with isoniazid 10 mg/kg/day for 8–12 weeks (the incubation period), after which the TST or IGRA should be repeated and, if still negative, the chemoprophylaxis should be stopped.

However, **if it becomes positive,** if the child is asypmptomatic and if the chest X-ray is negative, the child should be considered as having LTBI, and the chemoprophlylaxis should be continued for a total of 6–9 months (if the child is immunocompetent) or 12 months (if the child is immunocompromised) [34,35]. On the other hand, if the

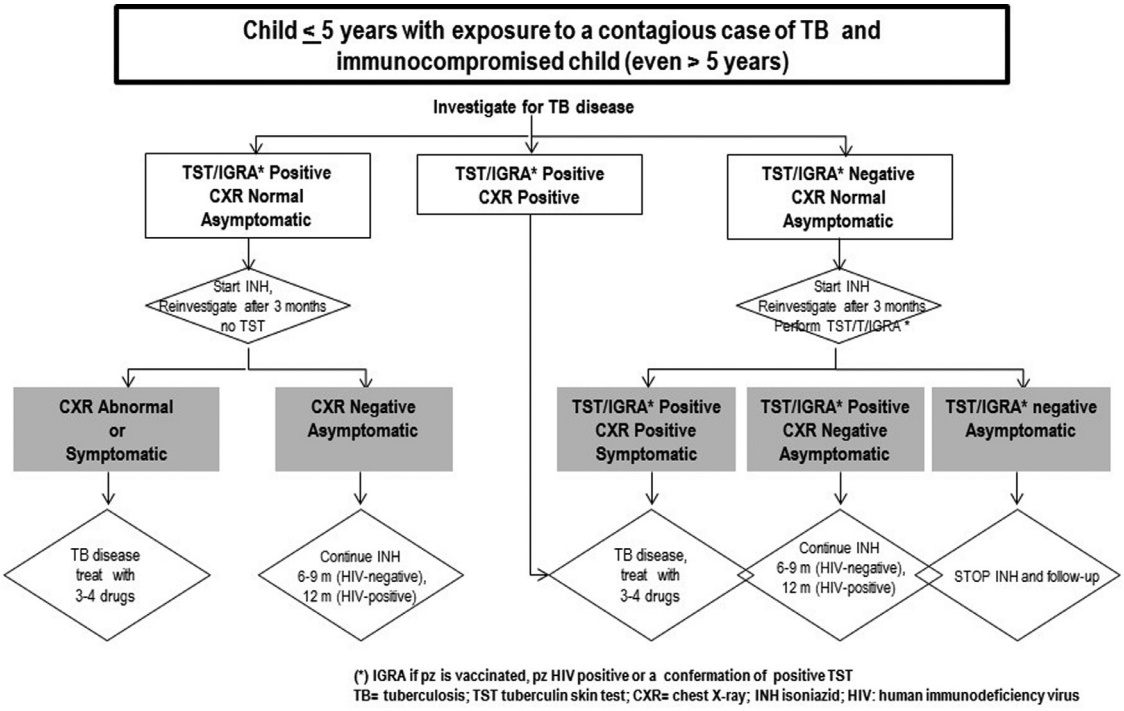

Fig. 1. Management of children aged ≤5 years exposed to a case of TB and exposed immunocompromised children of any age.

TST/IGRA becomes positive, and the child is symptomatic and/or the chest X-ray is abnormal, the diagnosis of TB is likely [36].

If the contact is an HIV-infected child, isoniazid prophylaxis should be considered regardless of age [34,35].

Fig. 1 summarises the management of children aged ≤5 years exposed to a case of TB and the management of exposed immunocompromised children of any age.

Children aged >5 years who have been exposed to a case of contagious TB must also be investigated in order to exclude tuberculous infection [5]. If the TST or IGRA and chest X-ray are negative, it is not necessary to start primary chemoprophylaxis unless the child is immunocompromised (in which case, isoniazid should be administered for 8–12 weeks) [5], and all of the children should undergo a repeat TST or IGRA 8–12 weeks after the first. The children with a positive initial TST or IGRA should undergo chest radiography and, if the X-ray is negative and the child is asymptomatic, the diagnosis is LTBI and preventive isoniazide chemotherapy should be started; if the test is negative, no treatment is necessary. If the TST or IGRA is positive, the patient is symptomatic and/or the chest X-ray is pathological, the diagnosis is tuberculous disease and specific treatment should be started.

Fig. 2 summarises the management of children aged > 5 years exposed to a case of TB.

An exposed asymptomatic child does not have to be kept away from school or prevented from playing with other children [5]. As stated above, unlike adults, children with TB are rare contagious for various reasons: first of all, they often have paucibacillar disease that leads to a low index of positivity for resistant acid-fast bacilli (AFB) in respiratory samples [37]; secondly, they less frequently have cavitating pulmonary forms partially because of their immature immune response [38]; thirdly, the cough of prepubertal children is less violent and less productive that of adults, and aerolization is reduced [39]; fourthly, pediatric TB is more frequently extra-pulmonary than the TB encountered in immunocompetent adults [1,40–42].

However, there are various reports of TST conversion in healthcare personnel exposed to breastfeeding infants with congenital miliary TB [38,39]. These children had a high bacilliferous load and, furthermore, the TB was initially unsuspected, which led to delays in its diagnosis and the isolation of the patient. As a general rule, all children with specific symptoms and radiographic characteristics of pulmonary TB similar to those observed in adults should be considered potentially contagious.

How is childhood latent tuberculous infection (LTBI) defined, and how should it be treated and monitored?

LTBI is defined as the condition created when *M. tuberculosis* has entered the body and stimulated an immune response [1]. The only sign of LTBI is a positive TST or IGRA. A child with LTBI has a positive TST and/or IGRA, no clinical sign of disease, and a chest X-ray that may be normal or reveal the presence of a remote infection such as nodular parenchmal calcifications or calcified intra-thoracic lymph nodes. People with LTI are not contagious [1].

It has been estimated that about one-third of the world's population are carriers of latent *M. tuberculosis* [1]. Immunocompetent subjects with LTBI have a 10% lifetime risk of developing TB, and half of these will develop the disease within 2–5 years of being infected, but the risk is significantly greater in immunocompromised subjects, being 5–10% per year of life in those co-infected with HIV [1].

The rationale underlying the treatment of LTBI is based on the possibility of eliminating dormant bacilli, thus reducing their activation and the development of active disease. Preventive chemotherapy involves the administration of isoniazid at a dose of 10 mg/kg/day (maximum dose: 300 mg/day) for at least six months [1] but, as some studies have shown that the treatment is less efficacious if administered for less than nine months, many countries recommend treatment for at least this length of time [36]. A Cochrane review has shown that treating LTBI with isoniazid reduces the risk of pulmonary and extra-pulmonary TB and the related deaths, but there does not seem to be any significant difference in the efficacy of 6- and 9-month treatment [43]. Some European countries have proposed short-term chemoprophylaxis with isoniazid (10 mg/kg/day, maximum dose 300 mg/day) and rifampicin (10 mg/kg/day, maximum dose 600 mg/day) for 3–4 months, which has led to promising results

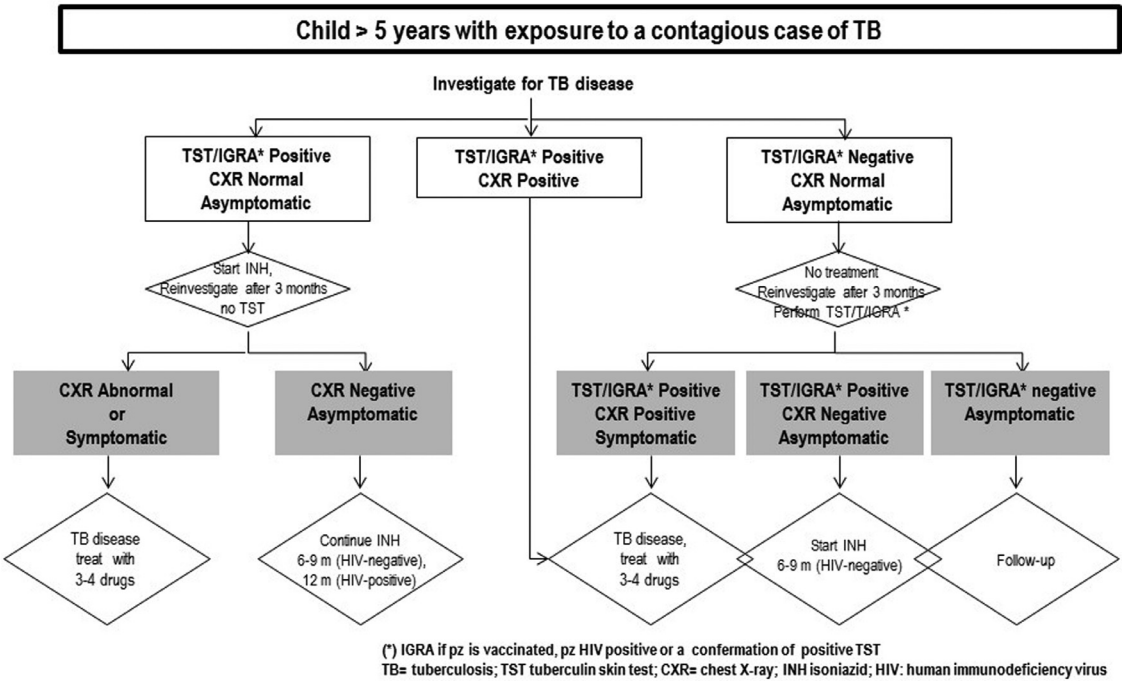

Fig. 2. Management of children aged > 5 years exposed to a case of TB.

in both children and adults [44]. Its efficacy seems to be equivalent to that of isoniazid monotherapy, but compliance is improved.

Routine laboratory monitoring is not recommended for children receiving isoniazid alone [5], but laboratory tests should be carried out if signs or symptoms of possible adverse events appear. In the case of hypertransaminasemia, no action is necessary unless transaminase levels are more than five times above the upper normal limit; however, if they are above this level, treatment should be discontinued [35]. Isoniazid chemoprophylaxis should be resumed once the results of liver function tests have normalised and the symptoms of toxicity have disappeared. The administration of pyridoxine (vitamin B6) 10–25 mg/day is recommended in the case of breastfeeding infants, and children with diabetes, HIV infection, malnutrition or peripheral neuropathy [36].

How should a child who has come into contact with a case of multidrug-resistant (MDR-TB) or extensively drug-resistant TB (XDR-TB) be managed and treated?

As only a few studies have analysed the usefulness of prophylaxis in the contacts of patients with MDR-TB (particularly in the pediatric population), there is insufficient evidence concerning the efficacy of the different post-exposure management and prophylactic strategies [35]. Close contacts such as family members are at greater risk of infection because of the frequency or duration of their contacts, which may have lasted weeks or even months before the index case has been diagnosed treatment has been started [5]. In their recent retrospective study cohort of 1,299 children in the families of patients with TB-MDR in Peru, Becerra et al. analysed the risk of developing TB and concluded that the risk was more than 30 times higher than in the general population [45]. The screening of relatives and other close contacts is therefore highly recommended in order to diagnose new cases early and prevent further transmission [46].

The available literature is concordant concerning the risk evaluation of children who have come into contact with MDR-TB patients [34,35,47-52]. Once the presence of active disease has been excluded, the probability of infection should be assessed by combining TST and IGRA results, and determining the duration and type of exposure to the index case and primary chemoprophyaxis can be started only in high-risk categories of MDR-exposed children.

Seven observational studies involving a total of more than 200 children have investigated the usefulness of primary chemoprophylaxis [53-58]. Kritski et al. retrospectively analysed 134 adults and 84 children aged 0–15 years who had come into contact with cases of MDR-TB in Rio de Janeiro, and found that the 45 contacts who had received prophylactic treatment with isoniazid 400 mg/day for six months were not significantly more protected [53]. Active disease was more frequently observed in male contacts ($p < 0.05$), those aged >15 years ($p < 0.001$), and those who had not been previously vaccinated with BCG ($p < 0.05$). It is worth noting that the contacts who developed the disease despite isoniazid prophylaxis were infected by *M. tuberculosis* strains resistant to isoniazid and rifampicin, and had had the same picture of resistance as their index case [54]. In the setting, Sneag et al. retrospectively showed that primary prophylaxis with isoniazid or a combination of isoniazid, rifampicin and pyrazinamide did not prevent the development of the disease in five child contacts [54]. According to the authors, it may worth considering 6–12 months chemoprophylaxis with at least two second-line drugs to which the isolate of the index case has proved to be sensitive.

A South African study of 105 child contacts of cases of MDR-TB found a significant difference between observation alone and the administration of multi-drug chemoprophylaxis based on the sensitivity of the strain isolated in the index case: only 5% of the treated children developed active disease as against 20% in the control group [55]. The prophylactic strategies included isoniazid (15–20 mg/kg/day), pyrazinamide (25–35 mg/kg/day), ethionamide (10–15 mg/kg/day) and/or ethambutol (15–20 mg/kg/day) and/or ofloxacin (15 mg/kg/day).

In their recently published cohort study, Seddon et al. demonstrated the good tolerability and efficacy of combined chemoprophylaxis with high-dose ofloxacin, ethambutol and isoniazid for six months in 186 children aged < 5 years or with HIV infection who had been exposed to MDR-TB [56].

Pineiro Perez et al. prospectively followed up nine children who had come into contact with the same case of MDR-TB every three months for two years, during which no case of TB was observed

Table 3
International guidelines for managing children who have come into contact with a case of MDR-TB.

Guidelines	Primary chemo- prophylaxis recommended?	Type of chemo-prophylaxis (if recommended)	Comments
Joint statement of the US Centers for Disease Control and Prevention, the American Thoracic Society, and the Infectious Diseases Society of America, 1992 [47]	Yes	Chemoprophylaxis including two drugs to which the strain of the index case is sensitive	
Partners in Health, 2003 [48]	No		The routine use of primary chemo-prophylaxis is not recommended because of the lack of data. However, the child should be closely monitored and, in the case of clinical worsening, treatment should be started bearing in mind the sensitivity profile of the strain isolated in the index case.
WHO, 2014 [34]	No		After being screened in order to exclude active disease, the child should undergo regular clinical monitoring for at least at least two years and closely observed for the onset of active disease
American Academy of Pediatrics, 2009 [35]	Yes	Combined primary chemoprophylaxis is recommended, with preference given to pyrazinamide, ethambutol and fluoroquinolones	
NICE, 2011 [49]	No		Clinical follow-up is recommended
Department of Health, Republic of South Africa, 2011 [50]	Yes, for children aged < 5 years	Chemoprophlaxis with high doses of isoniazid (15 mg/kg) is suggested for children aged < 5 years	
Al-Dabbagh M et al., 2011 [51]	Yes	Chemoprophylaxis for 9–12 months using at least two drugs (preferably pyrazinamide and a fluoroquinolone); the choice should be guided by the sensitivity of the strain isolated in the index case.	A strict follow-up is recommended in all cases. Prophylaxis should be started immediately in children aged < 4 years whereas, in those aged ≥4 years, it may be reasonable to wait until the TST has been repeated 8–12 weeks after the time of contact.
Seddon JA et al., 2012 [52]	No		A rigorous follow-up is recommended in order to identify the possible onset of disease early.

[57]. They therefore suggested that an optimal management strategy was close patient monitoring with a clinical evaluation every three months and a chest X-ray every six months. Watchful waiting has also been advised by Fred et al., who recommended close monitoring over time as the preferential approach [58].

A retrospective analysis of 10 children prophylactically treated with different regimens after coming into contact with patients with MDR-TB between 2004 and 2008 found that the only child with LTBI developed active disease because of inadequate treatment on the basis of the resistance profile of the isolate of the index case [59]. The authors suggested that contacts should be monitored and only be given LTBI prophylaxis based on the drug-resistance profile of the strain isolated in the index case.

In brief, although the findings of these studies do not allow any definite conclusions to be drawn, the results suggest that chemoprophylaxis can be advantageous in children exposed to MDR-TB, particular those at greater risk of developing active disease [52].

There are some considerable differences among the international guidelines concerning the management of children exposed to MDR-TB (Table 3). Four of the eight guidelines do not recommend the routine use of chemoprophylaxis on the grounds that the available data are insufficient [34,48,49] and, although the remaining four do recommend prophylaxis, they suggest different approaches [35,47,50-52]. The South African guidelines recommend treating all asymptomatic child contacts aged < 5 years with high-dose isoniazid (15 mg/kg) [50]. The USA suggest individualised multi-drug regimens based on the sensitivity of the strain isolated in the index case, with pyrazinamide, ethambutol or a fluoroquinolone being considered pharmacological options [35]. A joint declaration by the US Center for Disease Control and Prevention, the American Thoracic Society and the Infectious Diseases Society of North America, as well as the Canadian guidelines recommend that high-risk contacts should promptly receive primary chemoprophylaxis with two anti-tubercular drugs to which the strain isolated in the index case is sensitive [47,51], with preference being given to pyrazinamide and a fluoroquinolone. However, all of the guidelines agree that children exposed to a case of MDR-TB should be rigorously followed up.

Among the authors of the main reviews of the subject, Seddon et al. advise the use of chemoprophylaxis with isoniazid and a fluoroquinolone for at least six months in selected cases (e.g. children infected with HIV and/or those aged <5 years [52], whereas others suggest watchful waiting [60-62].

Table 4 lists the drugs used for post-exposure chemoprophylaxis, although there is limited data concerning their tolerability and adverse events, or their efficacy in children with MDR-TB [63]. Ettehad et al. have recently published a meta-analysis of eight studies involving a total of 315 children describing therapeutic outcomes [64]. Adverse events at the time of the use of anti-tuberculosis drugs were reported in 39.1% of cases: the most frequent was nausea, but the others included hearing loss (9–10%, with amikacin or capreomycin), psychic disorders (10.5-12.5%, with cycloserine), hypothyroidism (7.9–9.1%, with ethionamide), reduced visual acuity (9.1–12,5%, with ethambutol), increased creatinine kinase/muscle pain (9.1–12,5%, with amikacin or capreomycin) and tendinitis (12.5%, with levofloxacin).

Using a first-line, oral anti-TB drug to treat the contacts of a patient with MDR-TB may be questioned because of the possible resistance of the strain responsible for the index case [52]. However, only a few of the second-line oral drugs are available in pediatric formulations, and this could lead to dosing errors and the consequent risks of inefficacy or toxicity and lack of compliance. Furthermore, little is known about the pediatric pharmacokinetics of this class of drugs [52]. Although the latest-generation of fluoroquinolones (e.g. levofloxacin and moxifloxacin) have proved to be more efficacious in vitro than their predecessor (ofloxacin) [52], their use in children has been insufficiently studied [65,66], and the recent increase in their use to treat non-tuberculous infections in adults has raised concerns about a potential increase in bacterial resistance. Consequently, the

Table 4
Suggested chemoprophylactic drugs for children who have come into contact with a case of MDR-TB.

Drugs	Characteristics	Suggested dose	Unwanted effects	Comments
First-line oral antitubercular drugs				
Isoniazid	Inhibits the synthesis of the cell wall of mycobacteria by inhibiting the synthesis of mycolic acid; bacteriocidal; rapidly absorbed; high tissue distribution	Standard dose: 10 mg/kg once a day (up to a maximum of 300 mg/day) High dose: 15–20 mg/kg once a day (up to a maximum of 400 mg/day)	(Rare) Hypersensitivity; gastrointestinal disorders; peri-pheral neuro-pathy (due to reduced pyri-doxine levels); hepatitis. Well tolerated even at high doses.	In the case of risk factors for peri-pheral neuro-pathy (e.g. mal-nutrition, HIV infection, dia-betes), give pyridoxine (10–50 mg/day). Better absorbed if taken an empty stomach.
Rifampicin	Bactericidal; inhibits DNA-dependent RNA poiymerase; high tissue distribution.	10–20 mg/kg once a day (maximum 600 mg/day)	Hepatitis; reddish colour of secretions.	High rate of resistance. Better absorbed if taken an empty stomach.
Ethambutol	Bacteriostatic (bactericidal at high doses); inhibits cell wall synthesis; generally good absorption and distribution, but not in cerebro-spinal fluid.	15–25 mg/kg once a day (maximum 1.5 g/day)	Optical neuritis; peripheral neuropathy; hypersensitivity; gastrointestinal disorders.	Resistance rare (but difficult to evaluate). Efficacious. Visual field and colour vision need to be monitored. Not registered for administration to children aged < 5 years.
Pyrazinamide	Bacteriostatic; well absorbed and widely distributed; active at low pH.	15–30 mg/kg once a day (up to a maximum of 2 g/day).	Hepatitis; hyper-uricemia; myal-gia; arthralgia; rash; photo-sensitivity; gastrointestinal disorders. Adherence may be limited by severe side effects des-cribed in adults.	Unwanted effects may be reduced if taken with food. Rapid liver function monitoring required. Stop any hepatotoxic treatment if there are signs of hepatitis.
Group 2: Fluoroquinolones (ofloxacin, levofloxacin, moxifloxacin) N.B. Not registered for pediatric use	Bactericidal activity; inhibition of DNA gyrase; well absorbed and widely distributed.	Ofloxacin: 15–20 mg/kg once a day (maxi–mum dose 900 mg/day). Levoflaxin: 10–25 mg/kg once a day (maxi–mum 1000 mg/day). Moxifloxacin: 10 mg/kg once a day (maxi–mum 400 mg/day)	Sleep disorders; arthralgia; gastrointestinal disorders; peri- pheral neuro-pathy; headache; possible photo-sensitivity (levo-floxacin); long QT syndrome.	To avoid excessively alkaline urine, patients should be advised to increase their fluid intake. The efficacy of levo-floxacin during the latent phase may make it suitable for prophylaxis. Fluoroquinolones are the drugs of choice in adults with TB-MDR and TB-XDR.
Group 3: Injectable antitubercular drugs (aminoglycosides: amikacin, kanamycin, streptomycin; polypeptides: capreomycin, viomycin) N.B. Not all registered for pediatric use	Bactericidal action with high degree of extra-cellular activity; both categories inhibit protein synthesis	Amikacin: 15–20 mg/kg twice a day (maxi–mum 1000 mg per dose). Kanamycin: 15 mg/kg. Streptomycin: 20–40 mg/kg/day (adults 15 mg/kg/day), up to a maximum dose of 1 g/day; only intramuscular. Capreomycin: 15–30 mg/kg/day (adults 1 g/day, do not exceed 20 mg/kg/day)	Nephrotoxicity; ototoxicity; muscle pains; kypokalemia	Aminoglycosides do not cross the blood/brain barrier. Resistance to streptomycin is very frequent and the resistance evaluation test unreliable. High risk of major adverse events.
Group 4: second-line oral antitubercular drugs: thioamides (ethionamide and protionamide); cycloserine (and its terizidone derivative) N.B. Not registered for pediatric use	Ethionamide and protionamide: bacteriostatic; well absorbed and widely distributed; inhibit cell wall synthesis by inhibiting mycolic acid. Cycloserine: bacteriostatic, competitively inhibits the enzymes involved in the constitution of the cell walls of mycobacteria.	Ethionamide and protio-namide: 15–20 mg/kg/day in three daily doses (maxi–mum 1 g/day). Cycloserine:15 mg/kg/day in three daily doses (maxi–mum 1 g/day)	Ethionamide and protionamide: gastrointestinal disorders; hepa-titis; metallic taste I the mouth; hypothyroidism; hypersensitivity; hypoglycemia. Cycloserine: psychotic reactions; visual difficulties.	Ethionamide and protionamide: it is essential to monitor liver and thyroid function. In the case of severe gastro-intestinal disorders, administer other treatments separately while decreasing the daily dose, or start with a low dose and increase it over time
Group 5: less efficacious or less widely studied drugs (clofazimine, linezolid, clarithromycin) N.B. Not all registered for pediatric use	There are few data concerning the use of this heterogeneous group of drugs in the treatment of TB.	Clofazimine: 50 mg on alternate days in children aged < 10 years or 50–100 mg/day in adolescents and adults. Linezolid: 10 mg/kg three times a day, up to a maximum of 600 mg/day. Clarithromycin: 15 mg/kg/day in two doses, up to a maxi–mum of 500 mg per dose.	Clofazimine: photosensitivity; gastrointestinal disorders. Linezolid: dia-rrhea; nausea; vomiting; ane-mia; thrombo-cytopenia; opti-cal and peri-pheral neuritis. Clarithromycin: well tolerated.	The pediatric safety and effi-cacy of clofazi-mine have not been esta-blished; further-more, it is not readily available. The use of line-zolid should be reserved for the severe cases (e.g. resistant to > 7 anti-tubercular drugs), and hemochrome should be monitored. Its poor efficacy means that the role of clarithro-mycin is not clear.

Table 5
Use of molecular typing in analysing epidemics.

Technique	Discriminating power	Time of execution (strain)	Difficulty of interpreting data	Execution using positive excreted/ aspirated gastric material
Spoligotyping	Low	48 h	Low	Yes
24-loci MIRU-VNTR typing (current gold standard)	High (mediium for Beijing lineage)	48 h	Low	No; a partial profile can be obtained from positive samples
IS6110-RFLP Typing	High (low for strains with < 6 IS6110 copy numbers)	5–6 weeks	Medium–high	No
WGS	High	5–6 days	Medium–high	No

WGS= *whole-genome sequencing.*

American Academy of Pediatrics recommends restricting the pediatric use of fluoroquinolones to selected cases for which there is no safe and effective pharmacological alternative [65].

The administration of combinations of anti-tuberculous drugs may have some advantages: a standard regimen may not be universally appropriate, but individualised regimens based on the susceptibility profile of the strain isolated in the index case could increase the probability of efficacy and reduce the probability of resistance. However, the extensive testing necessary would require a similar effort to that of treating the disease itself and the costs per patient (and for national health services) have not been evaluated. Furthermore, as clinical monitoring would be fundamental in order to determine the response to either single-drug or combined prophylaxis, identify adverse events promptly and promote compliance, a strict follow-up during the 24 months following contact, with the rapid identification and treatment of developing TB may be a reasonable alternative [34,49].

In conclusion, the use of primary chemoprophylaxis in children exposed to MDR-TB remains a subject of debate. Its efficacy has been evaluated in only a few studies, none of which was a randomised and controlled clinical trial. Although some of the data seem to indicate an advantage, particularly in specific subgroups of contacts at high risk (the immunocompromised and children aged ≤5 years), there is no agreement in the literature concerning the preferred regimen. Close contacts are more likely to become infected and using the susceptibility profile of the strain isolated in the index case should be considered when making decisions concerning chemoprophylaxis.

How should molecular typing be used when analysing epidemics?

In order to be able to adopt efficient control measures, it is crucial to understand the transmission mechanisms and pathways of the *M. tuberculosis* strains causing epidemics, but the analysis needs to be made as soon as isolates become available if it is to be an effective aid to classic epidemiological studies [67]. As childhood pulmonary TB is typically paucibacillar and therefore not very infectious, it is generally believed that children rarely represent the index case of an epidemic, which is more likely to be one of their adult or adolescent contacts.

Molecular typing can be used to reconstruct the chains of transmission involving children when a clinical isolate is available (culture-positive cases) and so, in addition to abvious reasons of diagnosis, every effort should be made to obtain a cultured isolate.

The main molecular typing techniques are spoligotyping, IS6110-RFLP typing, MIRU-VNTR typing, and the analysis of punctiform mutations by means of new-generation whole-genome sequencing (WGS) [68,69]. Table 5 briefly summarises the discriminatory power and execution/response times of each of these techniques. They currently almost always need to have a strain isolated in culture in order to be able to obtain sufficient high-quality genomic material, but it is possible that future improvements in technology sequencing will allow reliable and epidemiologicaly useful results to be obtained from a microscopically positive sample.

A spoligotyping analysis can already be directly made using such a sample provided it contains more than 10^4 mycobacteria/mL, but its discriminatory power is relatively low regardless of whether a cultured sample or genomic material is used and, although it may be useful when it is necessary to exclude the possibility that a sample belongs to an epidemic cluster, this prevents it from being used to an epidemiological link [68,70]. It cannot distinguish different strains of the same family, and the clearly identifiable Beijing profile is predominant in many eastern European and south-eastern Asian countries.

The new gold standard for analysing epidemic foci (which has replaced IS6110-RFLP s 24-locus MIRU-VNTR typing, which has to be carried out by reference centres validated by an external quality control agency. The technique may be automated or carried out manually but, in both cases, reference strains have to be included in order to control the quality of the findings [69]. If the isolated strain belongs to the Beijing family, its MIRU-VNTR profile does not confirm that it belongs to the epidemic cluster unless there is clear evidence of contact: a second level of analysis is necessary that requires the evaluation of four hyper-variable loci in addition to the standard 24 [71]. Strains with different MIRU-VNTR profiles in two or more loci do not belong to the same recent chain of transmission, but strains with only one different locus may belong to the same cluster, particularly if the locus is hyper-variable [71,72].

The most recent literature shows that WGS typing techniques can provide a more reliable picture of transmission, especially in the case of large longitudinal clusters. If there are no epidemiological data indicating that contact has taken place, it is necessary to use WGS and single-nucleotide polymorphism (SNP) analysis to distinguish strains with identical MIRU-VNTR profiles. On the basis of the currently available data, strains with more than three different SNPs are considered not to belong the same cluster if the analysis is made using an appropriately filtered genome that excludes the hyper-variable repeat regions (PPE, PE_PGRS, ESX) responsible for increasing the number of SNPs unrelated to time-dependent genomic variations. The rather complex analysis of the data has to be made by a reference centre because both the quality of the sequencing and its interpretation may lead to misleading results by generating false clusters or excluding real transmissions [73]. It is possible that WGS will become the gold standard for the molecular analysis of epidemics.

Conclusions

On the basis of the published evidence and their own clinical experience, the group of experts reached the following conclusions:

(1) The following social, exposure and demographic factors must be considered **risk factors** for tuberculous infection and disease, and should be carefully considered when clinically evaluating pediatric patients with suspected TB:

Exposure factors

- Direct contact with TB patients **[III-A]**, particularly those who are expectorate/gastric aspirate positive and/or whose chest X-rays show signs of cavitating TB **[I-A]**;
- Immune impairment or cancerous diseases **[V-B]**.

- *Socio-economic, environmental and demographic factors*
- Socially disadvantaged conditions (e.g. over-crowding, homelessness, inadequate domestic ventilation) **[III-A]**;
- Low family income **[III-A]**;
- Illiterate or poorly educated parents (particularly mothers) **[III-A]**;
- Coming from a country that is highly epidemic for TB **[III-A]**.

The co-existence of two or more of the above factors significantly increases the risk of tubercular infection **[III-A]**. Their absence does not imply that there is no need to suspect TB.

(2) Subjects with the following conditions are at increased risk of developing TB:

- HIV infection **[I-A]**;
- Congenital immunodeficiency, particularly that involving T cells and the oxide reductase metabolism of phagocytes **[VI-A]**;
- Prolonged systemic corticosteroid therapy **[VI-A]**;
- Biological drug therapies **[VI-A]**;
- Oncological diseases **[I-A]**;
- Organ or tissue transplantation **[VI-A]**;
- Malnutrition **[VI-A]**.

(3) The contacts of cases of TB should be sought using the method of concentric circles based on the duration of exposure and the volume of the shared environment, with priority given to the contacts who have spent at least eight hours with the index case in an enclosed space or who are at greater risk of developing the disease **[III-A]**. The available means of screening contacts for TB are a TST, an IGRA and a chest X-ray **[III-A]**. The available evidence does not support using an IGRA as an alternative to a TST **[III-B]**.

Children aged ≤5 years who have been exposed to a case of pulmonary TB should undergo a TST, an IGRA and chest radiography in order to exclude tuberculous disease **[III-A]**. If the TST, IGRA and chest X-ray are negative, primary chemoprophylaxis with isoniazid 10 mg/kg/day should be given for 8–12 weeks (throughout the period of incubation), and the TST and IGRA should be repeated; if they are still negative, the chemoprophylaxis should be stopped **[III-A]**. However, if they have become positive, but the child is asymptomatic and a chest X-ray is negative, he or she should be considered as having LTBI and preventive chemotherapy should be continued (for a total of 6–9 months if the child is immunocompetent or 12 months if the child is immunocompromised) **[III-A]**. If the TST/IGRA become positive and the patient is symptomatic or the X-ray findings are abnormal, the diagnosis of tuberculous disease is to be considered likely **[III-A]**.

Children aged >5 years who have been exposed to a case of pulmonary TB should also be tested in order to exclude tuberculous infection **[III-A]**. If the TST, IGRA and chest X-ray are negative, primary chemoprophylaxis is not necessary unless the child is immunocompromised, in which case isoniazid treatment should be given for 8–12 weeks **[III-A]**. After this period, all exposed children should undergo another TST and IGRA in order to exclude tuberculous infection **[III-A]**. If these are negative, no treatment should be started but, if the tests are positive, a chest X-ray is required **[III-A]**. If the X-ray is negative and the child is asymptomatic, he or she should be diagnosed as having LTBI and isoniazid treatment should be started **[III-A]**. If the TST and IGRA are positive and the patient is symptomatic and/or the X-ray findings are abnormal, tuberculous disease should be diagnosed and specific treatment started **[III-A]**.

(4) A child with LTBI has a positive TST and/or IGRA, no clinical signs of disease, and a chest X-ray that may be normal or show evidence of remote infection **[III-A]**. The administration of isoniazid at a dose of 10 mg/kg/day (maximum dose 300 mg/day) for at least six months reduces the risk of pulmonary and extra-pulmonary TB, and the mortality associated with them **[I-A]**. Short-term preventive chemotherapy with isoniazid 10 mg/kg/day (maximum dose 300 mg/day) and rifampicin 10 mg/kg/day (maximum dose 600 mg/day) for 3–4 months seems to be as efficacious as isoniazid monotherapy and leads to greater compliance **[VI-B]**. Laboratory monitoring is not recommended for children taking isoniazid alone, but is required in the case of the onset of signs or symptoms of possible adverse events **[I-A]**. Pyridoxine (vitamin B6) should be given at a dose of 10–25 mg/day to breastfeeding infants and children with diabetes, HIV infection, malnutrition or peripheral neuropathy **[III-B]**.

(5) Primary chemoprophylaxis in the general population of children exposed to MDR-TB is not recommended because there are no studies that clearly show it is effective in preventing the progression to active TB, there is a risk of drug-related adverse events, and there is also a risk that the selection of strains with an even narrower spectrum of sensitivity will reduce possible future therapeutic options if active disease develops **[V-C]**. In such cases, a reasonable approach is to monitor the child closely for 24 months in order to identify and treat developing TB promptly **[V-B]**. Primary chemoprophylaxis can be considered for specific subgroups of children at high risk of developing a severe clinical picture, such as those who are immunocompromised or aged <5 years **[V-B]**; in these cases, the prophylactic regimen should be chosen on the basis of in vitro tests of the sensitivity of the strain isolated in the index case **[V-B]**.

(6) In order to be able to adopt efficient control measures, it is crucial to clarify the transmission mechanisms and pathways of the *M. tuberculosis* strains that cause epidemic foci and, to this end, an aliquot of every positive culture should be sent a reference centre **[VI-B]**. Molecular typing should always be used to confirm or exclude transmission, and intensify control measures **[VI-B]**.

Conflict of interest

The authors have no potential conflict of interest to declare.

Acknowledgements

This review was supported by a grant from the Italian Society for Pediatric Infectious Diseases (SITIP) and the Italian Ministry of Health (Bando Giovani Ricercatori 2009) grant No. GR-2009-1596786.

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